

REMARKS

Claims 16, 18-25, 36, 41-42, 44-47, 55-60, 62-64, 66-72, 74-80, 82, 83 and 85-88 were pending as of the issuance of the Office Action. Claims 22, 36, 41, 42, 44-47, 55-60, 62, 63, 75-80, 82, 83, 87 and 88 were withdrawn as set forth in the Office Action. Claims 16, 18-21, 23-25, 64, 66-72, 74, 85 and 86 stand rejected. By the current Amendment to Claims, claims 16, 20, 21, 22, 25, 36, 59, 85 and 86 have been amended.

Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed. The claims have been amended generally to attend to formal matters. In particular, claim 36 has been amended, in part, to include the limitations of pending claim 20.

No new matter has been added by the amendments to the claims. Applicants respectfully request that the aforementioned amendments be entered. Applicants note that the foregoing amendments have been made solely in order to expedite examination and in no way should be construed as acquiescence to the validity of the rejections set forth in the Office Action. Applicants reserve the right to pursue the claims as originally filed in this or subsequently filed applications. Following entry of the foregoing amendments, claims 16, 18-25, 36, 41-42, 44-47, 55-60, 62-64, 66-72, 74-80, 82, 83 and 85-88 will be pending.

Allowability of SEQ ID NO:35

The Examiner indicates that “[t]he indicated allowability of SEQ ID NO:35 is withdrawn in view of ADAMS... relied upon in the rejection below.” Applicants respectfully disagree with the Examiner’s assertion and will address the substance of such rejection in further detail below.

Election/ Restrictions

The Examiner indicates that “claims 22, 36, 41, 42, 44-47, 55-60, 62, 63, 75-80, 82, 83, 87 and 88 have been withdrawn pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/ species.”

Applicants respectfully note that claims 36, 41, 42, 44, 45, 46 and 47 are method claims that depend from or otherwise include all the limitations of pending composition claim 20. Accordingly, pursuant to the provisions of MPEP § 821.04,

Applicants respectfully request rejoinder of claims 36, 41, 42, 44, 45, 46 and 47 in the event that pending composition claim 20 is found to be allowable.

Sequence Compliance

The Examiner advises that the application is not in compliance with 37 CF §§ 1.821 – 1.825 on the grounds that

Applicant's sequence listing and claims are inconsistent with each other. Claim 16, 20, 21, 22, 36, 85 and 86 recite SEQ ID NO:2, however many of the limitations of SEQ ID NO:2 in the claims are not allowed when one looks to the sequence listing. For example, the sequence listing does not allow for deletion of amino acids in SEQ ID NO:2, nor does it allow for alternative amino acids (substitutions) for a defined amino acid. Additionally, modifications such as reversal of amino acids (e.g. F and X5) is not allowed by the sequence rules, as such modified peptides are structurally distinct and thus require a unique SEQ ID NO. Additionally, it is improper to identify a substitutable position by a specific amino acid and then indicate that it can be something else (e.g. claim 85 options (b), (d), (f) and (g)). Applicant is reminded that a single sequence identifier cannot be used to define multiple sequences. Here, it appears to the examiner that claim 16 is consistent with the sequence listing as the 'wherein' clause adds further limitations on what is allowed by SEQ ID NO:2. In contrast, as exemplified above, claim 85 is not supported by the sequence listing, and lacks antecedent basis to the sequence listing, as the modifications are beyond those contemplated or allowed in the description of SEQ ID NO:2 therein.

Additionally, sequences are recited in the Figures without corresponding SEQ ID Nos, e.g. Figure 6.

Applicants respectfully disagree. Notwithstanding the foregoing, Applicants submit that an updated sequence listing and appropriate amendments to the specification (to introduce sequence identifiers) will be filed shortly, in accordance with the Examiner's recommendations.

With respect to the Examiner's contention that "sequences are recited in the Figures without corresponding SEQ ID NOs, e.g. Figure 6," Applicants submit that the foregoing amendments to the specification introducing sequence identifiers, presented in accordance with the Examiner's recommendations, render the foregoing objection moot.

Specification

The Examiner objects to the specification on the grounds that “[t]he specification relies upon the recitation ‘SEQ ID NO:2’ for numerous distinct sequences throughout the specification.” Applicants respectfully disagree. Notwithstanding the foregoing, Applicants submit that an updated sequence listing and appropriate amendments to the specification (to introduce sequence identifiers) will be filed shortly, in accordance with the Examiner’s recommendations.

The Examiner further objects to the specification for reference to the trademark “Reacti-BindTM”. Applicants submit that the foregoing amendments to the specification, presented in accordance with the Examiner’s recommendations, render the foregoing rejection moot.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objections to the specification.

Drawings

The Examiner objects to the drawings “because the figures recite sequences without corresponding SEQ ID NOs, e.g. Figure 6.” Applicants submit that the foregoing amendments to the specification introducing sequence identifiers, presented in accordance with the Examiner’s recommendations, render the foregoing objection moot.

Claim Objections

Claims 16, 20, 21, 85 and 86 are objected to for various formalities. Applicants submit that the foregoing amendments, presented in accordance with the Examiner’s recommendations, address such objections, and thereby render these objections moot. Specifically, Applicants have introduced a period at the conclusion of claim 25, amended claims 16, 20, 21, 85 and 86 to recite a colon as opposed to a semi-colon and, lastly, amended claim 85 to properly recite “1-naphthylalanine”. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding claim objections.

Rejection of Claims 20, 21, 64, 66-72, 74, 85 and 86 under 35 U.S.C. § 112, second paragraph

Claims 20, 21, 64, 66-72, 74, 85 and 86 are rejected under 35 U.S.C. § 112, second paragraph, “as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.”

Specifically, the Examiner rejects claims 20, 21, 64, 66-72, 74, 85 and 86 on the grounds that

...in view of the limitations in the claims, and dependent claims therein, claims 20, 21, 64, 66-72, 74, 85 and 86 lack antecedent basis as the sequence listing does not provide support for various modifications. SEQ ID NO:2 does not provide support for the various modifications, e.g. reversal of X₅ and F, substitution of L or F, etc. are not within the definition of SEQ ID NO:2.

Applicants respectfully disagree. Notwithstanding the foregoing, Applicants submit that an updated sequence listing and appropriate amendments with respect to sequence identifiers will be filed shortly, in accordance with the Examiner’s recommendations. Applicants submit that such updated sequence listing will render the foregoing rejection moot.

The Examiner further rejects claims 20, 21, 85 and 86 on the grounds that

Claim 20 indicates modifications (a), (b), (c) or (d) which is any combination of (a), (b) and (c), however the Markush group of the modifications is improperly presented, as in the current form, all must be present, as they are not in the alternative (lacking ‘or’ between the options), and are not set off as a proper Markush group (“selected from the group consisting of...”). Thus, it is unclear how one can have a combination of any of the three modifications when all three are required.

Claims 21, 85 and 86 recites ‘or’ between (f) and (g), however it is unclear as to how (g) is an alternative to (f), and how one selects the alternative. For example, is (g) the alternative to (f), or did Applicant intend ‘and’?

Applicants respectfully submit that the foregoing amendments to the claims render the foregoing rejections moot. Indeed, claims 20, 21, 85 and 86 have been amended to clarify the scope of the claimed invention.

Lastly, the Examiner rejects claim 85 on the grounds that

...claim 85 recites ‘(g) phenylalanine is replaced by...’, however it is unclear as to which phenylalanine it refers and thus lacks clear antecedent basis. The

peptide sequence contains phenylalanine (F) as the last amino acid and X5 recites phenylalanine, and thus it is unclear if Applicant is limiting the Markush selection of phenylalanine or the F residue of SEQ ID NO:2.

Applicants respectfully submit that the foregoing amendment to claim 85, presented in accordance with the Examiner's recommendations such that "(g) phenylalanine" has been amended to recite "(g) F", renders the foregoing rejection moot.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections of the pending claims under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 16, 18-21, 24, 25, 66-72, 74 and 85 under 35 U.S.C. § 102(b) (Adams)

The pending claims have been rejected as being anticipated by Adams *et al.* (*Molecular and Cellular Biology* (1996) 16(12):6623-6633) (hereinafter referred to as "Adams") on the grounds that Adams allegedly

teaches peptide sequences in Figure 2 (page 6625) that anticipate the instant claims, including KACRRLFG (p21(N)), HSKRRLIF (p21(C)) and SAKRRLFG (p107). The sequences are taught as being the putative cyclin-cdk2 binding regions.

It is noted that HSKRRLIF is instant SEQ ID NO:34 and KACRRLFG is instant SEQ ID NO:38 (claim 25).

Applicants respectfully disagree. Applicants submit that Adams fails to teach each and every limitation of the pending claims. The presently claimed invention is generally directed to ***a peptide of eight amino acid residues, as defined by the closed language "consisting of"***. The claimed sequences are thus limited as such, and do not include 3' or 5' amino acid residues to the recited formula $X_1X_2X_3RX_4LX_5F$. In view of the foregoing, Applicants submit that Adams fails to teach or suggest a peptide of eight amino acid residues consisting of the amino acid sequence of $X_1X_2X_3RX_4LX_5F$ as set forth in the pending claims.

Indeed, the amino acid sequences set forth in Adams (*i.e.*, KACRRLFG (p21(N)), HSKRRLIF (p21(C)) and SAKRRLFG (p107)) are merely putative binding motifs within a longer peptide and are not isolated eight residue peptides, as required by the pending claims. Figure 2 of Adams merely shows the sequence alignment of putative cyclin-cdk2 binding regions from multiple cell cycle regulators, in particular, alignment of putative cyclin cdk2 recognition motifs of each of E2F1, E2F2, E2F3, p107, p130, p21^{cip1}, p27^{klp1} and p57^{klp2}.

Adams further clarifies the nature of these teachings:

Multiple cell cycle regulatory, cyclin-binding proteins contain a sequence with homology to the cyclin A-cdk2 binding sequence of E2F1. Among these are two additional members of the E2F family, E2F2 and E2F3, the p21-like CDKI's p21, p27 and p57, and the putative substrates p107 and p130. **There are two such motifs in p21**, one at the N-terminus and one, unexpectedly in light of previously published data, at the C-terminus... **Fourteen residue synthetic peptides** spanning these sequences in p107, p130 and either N or C terminus of p21 likewise inhibited the binding of cyclin A to E2F, whereas scrambled versions of these peptides did not (Fig. 3A). (Adams, page 6625, columns 1-2).

Moreover, the Figure 3 legend further clarifies that these sequences are merely motifs in larger sequences by referencing CGS**KACRR**LFGPVD (p21N, wild type), DYF**H**SKRR**L**IFSKR (p21C, wild type) and TAGS**AKRR**LFGEDP (p107, wild type) (emphasis added).

Based on the foregoing, Applicants submit that Adams fails to directly and unambiguously disclose an isolated eight residue peptide sequence as set forth above in bold and as asserted by the Examiner. Accordingly, Applicants submit that Adams fails to teach each and every limitation of the claimed invention, *i.e.*, a peptide **consisting of** the amino acid sequence $X_1X_2X_3RX_4LX_5F$. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. § 102(b).

Rejection of Claims 16, 18-21, 23-25, 64, 66-72, 74, 85 and 86 under 35 U.S.C. § 103(a)

Claims 16, 18-21, 23-25, 64, 66-72, 74, 85 and 86 have been rejected as being unpatentable over Adams in view of U.S. Patent No. 6,777,388 (Grasso *et al.*) (hereinafter referred to as “Grasso”), U.S. Patent No. 6,310,040 (Bozyczko-Coyne *et al.*) (hereinafter referred to as “Bozyczko-Coyne”) and U.S. Patent No. 5,639,726 (Lawrence *et al.*) (hereinafter referred to as “Lawrence”). In particular, the Examiner is of the opinion that

[t]he instant claims and teachings of Adams are presented *supra*. The instant claims are additionally drawn to the peptides HAKRRLIF and HAKRRLIF-amide, as well as to general modification where an amino acid is replaced with its D-isomer or the alanine/serine is replaced with glycine.

Here, with regards to the peptide HAKRRLIF (SEQ ID NO:35) and the amide form (SEQ ID NO:28), the difference between the teachings of Adams and the instant claims is that Adams has a serine as X_2 , where SEQ ID NOs: 35 and 28 have alanine. In view of the teachings of Grasso, one would have

relied upon alanine scanning to determine the activity and importance of each side chain in the biological activity. Thus it would have been obvious to have synthesized the HAKRRLIF in order to determine the importance of the serine side chain on activity. One would have been motivated to have made such peptides in order to elucidate the importance of all residues, including the X₂ serine. The method of alanine scanning and peptide synthesis techniques required to form such peptides are well known and widely practiced in the art, and thus one would have had a reasonable expectation for success in making the peptide...

With regards to the amide form, it would have been obvious to have synthesized the amide form of the peptide to increase aqueous solubility of the peptide and to increase the stability of the peptide. One would have been motivated to have acetylated the peptide to increase the aqueous solubility of the peptide and to obtain the benefit of increased activity from the amidation. Amidation of peptides is a routine technique widely practiced in the peptide arts, and thus one would have had a reasonable expectation for success in making the peptide.

Applicants respectfully traverse the foregoing rejection for the following reasons. Specifically, Applicants submit that the teachings of Adams, alone or in combination with the teachings of Grasso, Lawrence or Bozyczko-Coyne, fail to teach each and every limitation of the claimed invention, as required for a proper obviousness rejection under 35 U.S.C. § 103(a).¹ Applicants submit that while Adams discloses fourteen residue peptides CGSKACRRLFGPVD (p21N, wild type), DYFHSKRRLIFSKR (p21C, wild type) and TAGSAKRRLFGEDP, Adams fails to teach or suggest the isolated peptides of eight amino acids, as set forth in the claims as pending. The Examiner's rejection is predicated upon the Examiner's contention that Adams allegedly teaches eight amino acid peptides. However, as argued above, Adams merely teaches putative binding motifs within a longer peptide and not isolated eight residue peptides, as required by the present claims. Moreover, Adams and/ or the state of the art fail to provide any teaching or suggestion that the claimed truncated sequences would retain desired kinase inhibitory activity or exhibit the selectivity for cdk2 over cdk4, as taught by the present invention.

The teachings of Grasso, Lawrence or Bozyczko-Coyne fail to account for the deficiencies of Adams in this regard. Indeed, neither Grasso, Lawrence or Bozyczko-Coyne teach or suggest the recited peptide, or, alternatively, provide the motivation or suggestion to modify the sequences of Adams to arrive at the claimed invention.

As such, the proposed combinations as set forth in the Office Action fail to teach or suggest each and every limitation of the claimed invention, as required for a

¹ As set forth in M.P.E.P. § 2143.03, "In order to establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art."

proper rejection under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 16, 18-21, 23-25, 64, 66-72, 74, 85 and 86 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants believe that no additional fee is due with this submission. However, if the Applicants are in error, the Commissioner is authorized to charge any deficiency in the fees paid herewith, or credit any overpayment, to Deposit Account No. 12-0080, under Order No. CCI-014RCE, from which the undersigned is authorized to withdraw.

If there are any remaining issues or if the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

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Respectfully submitted,

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